10. (amended) A method as claimed in claim 1, wherein ~~the concentration of compound~~ Luteolin is ~~ranging between~~ administered in an amount in the range of 1 to 10 mg/kg of body ~~weights~~ weight.

11. (amended) A method as claimed in claim 1, wherein ~~the duration of administering compound~~ Luteolin is administered for a time period ~~ranging between~~ in the range of 5 to 10 days.

12. (original) A method as claimed in claim 1, wherein compound Luteolin inhibits airway constriction.

13. (original) A method as claimed in claim 1, wherein compound Luteolin inhibits airway hyperactivity.

REMARKS

Claims 1-13 were examined and are pending in the present application. By this amendment, Claims 1, 2, 4 and 9-11 are amended, leaving Claims 1-13 pending.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1, 2, 4 and 9-11 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 has been amended as kindly suggested by the Examiner, to correct a grammatical error by adding the article "a" before the phrase "therapeutically effective dose ...."

Claim 2 was said to be indefinite for reciting the phrase "wherein the compound Luteolin shows no side effects" because the Examiner considers it unclear as to whether this refers to

"side effects" that are beneficial or adverse to the recipient of the compound. Claim 2 has been amended to specify a method wherein the compound Luteolin shows negligible side effects." Support for this amendment is provided in the disclosure, for instance, at page 1, lines 29-30, which teaches that "[t]he current focus in managing asthma is the control of inflammation using anti-asthmatic drugs with lower or negligible side effects (Barnes, 1999)." Applicant respectfully submits that it would be clear from this context to one of ordinary skill in the pharmaceutical arts that the reference to "negligible side effects" in the specification and Claim 2 would only comprehend negative side effects. Applicant is not aware of any source that would suggest to one of ordinary skill that the current focus in managing asthma (or any other disease) would be using drugs with lower or negligible ***positive*** side effects, as posited by the Examiner.

Claim 4 has been amended to address the alleged lack of antecedent basis for a method "wherein the development of asthmatic features ... are prevented," by reciting that "the method prevents development of asthmatic features ...."

Claim 9 has been amended to address the alleged lack of antecedent basis for a method wherein "the concentration of compound Luteolin...," and to correct minor grammatical errors, by reciting "wherein Luteolin is administered in an amount in the range of 0.1 to 10 mg/kg of body weight."

Claim 10 has been amended to address the lack of an upper range limit, as well as lack of antecedent basis alleged for Claim 9, for a method wherein "the concentration of compound Luteolin...," and to correct minor grammatical errors, by reciting "wherein Luteolin is administered in an amount in the range of 1 to 10 mg/kg of body weight." Support for this amendment is provided in the disclosure, for instance, in Example 2, page 8, lines 19-26 which

describes experiments in which Luteolin is administered to animals in the amount of 0.1, 1 or 10 mg/kg of body weight.

Claim 11 has been amended to address the alleged lack of antecedent basis for a method "wherein the duration of administering Luteolin," by reciting "wherein Luteolin administered for a time period in the range of 5 to 10 days."

In view of the above amendments which are believed to fully address each of the above objections and rejections to Claims 1, 2, 4 and 9-11, under 35 U.S.C. § 112, second paragraph, Applicant respectfully submits that each of these objections may properly be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 102(b)

Claims 1, 3, 4 and 9-10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Aoyama et al.

Claim 1 as presently amended specifies a "method of preventing and/or treating asthma in animals including humans using natural compound Luteolin, said method comprising administering a therapeutically effective dose of the Luteolin."

The Office Action asserts that the cited reference anticipates the claimed subject matter because (1) "Aoyama teaches a method of preventing and/or treating asthma in animals comprising orally administering an effective amount of an alcoholic extract obtained from the *Perilla* seed, which comprises Luteolin;" (2) "Aoyama teaches the reference extract as a histamine release inhibitor, which is extremely good in action of inhibiting the release of histamine or the development of asthmatic features comprising Early Airway Response (EAR);" and (3) "In [0027], Aoyama teaches administering 0.5-3000 mg/day of the reference extract or 0.3 to 15% weight percent or 0.01-10 weight percent to a patient in need thereof of treatment.

Regarding statement (1), above, Applicant respectfully notes (according to the English JPAB Abstract provided by the PTO) that what Aoyama actually disclosed about the alcoholic extract obtained from the *Perilla* seed is not simply that it "comprises Luteolin," but that it "contains one or more compounds selected from apigenin, chrysoeriol, luteolin and rosmarinic acid" (or "resomarinic acid," according to the Derwent English Abstract). The Examiner has not indicated, and Applicant has not been able to discern from the provided English abstracts and translation, any teaching in Aoyama of what amount of Luteolin (or of any other of the four named compounds), if any, was actually present in the disclosed extract. Accordingly, statement (3) above, that "In [0027], Aoyama teaches administering 0.5-3000 mg/day of the reference extract or 0.3 to 15% weight percent or 0.01-10 weight percent to a patient in need thereof...," at most represents a prediction of an amount of the uncharacterized extract that might be effective for the specified purpose, where the amount of each of the four named compounds (and probably many others in the extract) is not known. In fact, the inventor evidently admits that the composition of the disclosed extract may vary. See [0019; emphasis added] ("all of apigenin, chestnut SOERI oar [*sic*, chrysoeriol], luteolin and a loss marine [*sic*, resomarinic] acid are usually contained in the alcoholic extract....."

Applicant therefore respectfully submits that the cited disclosure in [0027] of Aoyama cannot be seen as disclosing even any predicted therapeutic amount of any single compound in the disclosed extract, and certainly not any effective amount of luteolin, in particular, that is predicted to have a specified effect. The cited disclosure certainly does not teach how much luteolin would constitute "a therapeutically effective dose" *in vivo*, for any therapeutic purpose. In short, the cited Aoyama disclosure does not describe or otherwise teach "a therapeutically effective dose" of luteolin, as required to anticipate Claim 1.

Further, statement (2) in the rejection, that "the reference extract ... is extremely good in action of inhibiting ... the development of asthmatic features comprising Early Airway Response (EAR)," evidently represents mere unsupported speculation by the Examiner, as the Examiner did not point out, and Applicant has not discerned, any disclosure in Aoyama that would support this conclusion, that Aoyama teaches that the extract is extremely good at inhibiting asthmatic features comprising Early Airway Responses. Further, considering Claim 4 in particular, which is directed to a method that prevents development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response (LAR), Applicant further notes that the Examiner has not even speculated that the disclosure of Aoyama would teach that luteolin, or even the extract, would prevent Late Airway Response (LAR) features of asthma.

Of particular importance is the fact that Aoyama, as Applicant understands this disclosure, tested the extract and various fractions of unspecified purity only *in vitro*, on certain rat cells, for "histamine suppression" (see, e.g., Derwent Abstract, Use and [0033]). The Examiner did not cite, and Applicant has not found, any indication in Aoyama that luteolin alone, or even the uncharacterized extract, was tested in any *in vivo* model at all, much less one relevant to asthma.

As evidence that demonstration of anti-histamine activity in a compound, such as allegedly disclosed by Aoyama for luteolin, is not sufficient to show effectiveness of that compound in treating asthma, Applicants direct the Examiner's attention to the case of the anti-histamines ketotofen and clemastine. According to Cockroft et al. (see Abstract provided herewith), in a clinical trial on human subjects with asthma, neither of these known anti-histamines produced a significant reduction in allergen-induced early or late asthmatic responses, or in the allergen-induced fall in methacholine responses, despite significant inhibition in a

histamine skin test endpoint. Accordingly, *in vitro* detection of anti-histamine activity of a compound, as in Aoyama et al., does provide evidence that the compound will necessarily be useful in preventing development of asthmatic features comprising either Early Airway Responses or Late Airway Responses.

In short, the disclosure of Aoyama, even according to the inaccurate description thereof in the Office Action, cannot anticipate present Claim 1, at least because Aoyama fails to disclose "a therapeutically effective dose" of the specific compound luteolin for any purpose, much less any evidence this specific compound necessarily would be useful for preventing or treating any features of asthma, as in the presently claimed method. In this context, Applicant wishes to respectfully remind the Examiner that anticipation, even inherent anticipation, requires that the "missing characteristic is necessarily present, or inherent, in the single anticipating reference." Schering Corp. v. Geneva Pharms., Inc., 1377 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

Further, since Claim 1 is not anticipated by Aoyama, at least because the required therapeutically effective dose of luteolin for preventing and/or treating asthma is missing from the disclosure, it follows that the other claims cited in this rejection, Claims 3, 4 and 9-10, also are not anticipated, because each of these claims depends from Claim 1 and, therefore, also includes the same requirement for a therapeutically effective dose of luteolin for preventing and/or treating asthma. Regarding the dosage range of luteolin specified for administration in Claim 9, however, Applicant is particularly at a loss to understand how the Examiner believes this range is taught by the Aoyama disclosure which evidently does not disclose or otherwise teach or suggest *in vivo* administration of any dosage of luteolin, as opposed to administration of an extract which may contain undetermined amounts of this compound.

Claims 1-3 and 12-13 also stand rejected under 35 U.S.C. § 102(b) as being anticipated by Peng et al. (U). According to the Examiner, "Peng teaches a method of treating asthma comprising orally administering an effective amount of luteolin to animals." In particular, the Examiner states that "Peng teaches [that] administration of luteolin showed a marked antitussive effect due to a direct action of luteolin on the cough center in the brain stem and to desensitization of certain sensory sites on the trachea," and that "luteolin caused relaxation of tracheal smooth muscle following acetylcholine- or histamine-induced contractions both in an *in vitro* and *in vivo* system." Finally, Peng is said to teach that "oral administration of luteolin did not cause death in mice."

Applicant respectfully disagrees with the Examiner regarding the conclusion that "Peng teaches a method of treating asthma comprising orally administering an effective amount of luteolin to animals." Thus, the translation of the title of the disclosure of Peng et al. does not indicate that the compound is effective as a treatment for asthma, only that the document describes "pharmacological studies on the antitussive expectorant and antiasthmatic effect[s] of luteolin ...." Further, as Applicant understands the disclosure of Peng (based on the English abstract provided with the Office Action, the document provides results of various *in vitro* and *in vivo* tests that might have relevance to certain symptoms of asthma, but the disclosure does not teach whether these results demonstrate that the compound ***is*** useful, ***may be*** useful or ***is unlikely to be*** useful for treating and/or preventing asthma according to the presently claimed method. The cited observation that "oral administration of luteolin did not cause death in mice," presumably indicating low toxicity in normal mice, likewise does not indicate whether the tested high doses of the compound, or any lower dose, would be safe and effective for treating asthma.

Applicant respectfully submits that the disclosure of Peng et al. must be read in light of the nature of asthma, the disease to be treated. Thus, as the present application teaches, asthma is an inflammatory disease of the airways that is characterized by difficulty in breathing due to constriction of smooth muscles of the bronchi as a result of inflammation. Page 1, lines 23-25. Accordingly, the fact that Peng et al. tested luteolin for "antitussive effects" in mice and cats is not informative about therapeutic effectiveness for asthma. Thus, the available disclosure provides no indication that the employed model are considered relevant to asthma as opposed to other conditions involving cough, and mere suppression of cough would do nothing to prevent or treat the inflammatory disease that is asthma, or the associated difficulty in breathing.

Similarly, the disclosure that unspecified dose(s) of luteolin administered by unspecified route(s) "caused relaxation of tracheal smooth muscle following acetylcholine- or histamine-induced contractions both in the *in vitro* and *in vivo* system" does not evidence what dose, if any, would be therapeutically effective in preventing or treating asthma *in vivo*, particularly absent any indication of relevance of the *in vitro* and *in vivo* systems to asthma. Thus, by omitting Claim 9 from this rejection the Examiner has conceded that the preferred dosage range for preventing or treating asthma recited in that claim (0.1 to 10 mg/kg body weight) is not disclosed or otherwise taught by Peng et al. Further, as noted above, a demonstration that a compound has anti-histamine activity in any model system, particularly at an unspecified dosage level, does not per se necessarily mean that the compound would be therapeutically effective for treatment of asthma. See, e.g., the discussion of the anti-histamines, ketotofen and clemastine, in Cockroft et al., *supra*.

In short, the disclosure of Peng et al. cannot anticipate present Claim 1, at least because it fails to disclose "a therapeutically effective dose" of luteolin as specified in the claim, by failing

to provide any evidence that this compound necessarily would be useful for preventing or treating any features of asthma, the inflammatory disease, as required in the presently claimed method. Again, Applicant would like to respectfully remind the Examiner that anticipation, even inherent anticipation, requires that the "missing characteristic is necessarily present, or inherent, in the single anticipating reference." 339 F.3d at 1377, 67 USPQ2d at 1668.

REJECTIONS UNDER 35 U.S.C. § 102(b) OR 35 U.S.C. § 103(a)

Claims 1-13 also stand rejected under 35 U.S.C. § 102(b) as anticipated by Aoyama et al. (N) or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Aoyama et al. (N) and Peng et al. (U) in view of Nagai (V), Park et al. (W) and Kimata et al. (X).

This rejection describes the disclosure of Aoyama as in the above rejection of Claims 1, 3, 4 and 9-10, but also admits that "Aoyama does not expressly teach that the reference method for prophylaxis and/or treatment of asthma in animals comprising administering luteolin encompasses modifying levels of IFN-gamma, IL-5, IL-4 and IgE to a normal level and inhibiting airway constriction and airway hyperactivity." The Examiner evidently believes, however that "the[se] claimed functional effects are inherent to the method taught by Aoyama since the instantly claimed method is a one-step process of administering a therapeutic dose of luteolin to a patient in need of prevention and/or treatment of asthma, and since the ingredient, the amount of the ingredient, and the route of administration for the delivery of the ingredient are the same as instantly claimed by Applicant."

In the alternative, "even if the claimed method is not identical to the referenced extract with regard to some unidentified characteristics," the Examiner evidently believes that "the differences between that which is disclosed and that which is claimed are considered to be so

slight that the referenced method is likely to inherently possess the same characteristics of the claimed method particularly in view of the similar characteristics which they have been shown to share," and therefore, "the claimed method would have been obvious to those of ordinary skill in the art within the meaning of USC 103."

Applicant respectfully notes, as pointed out above, that the disclosure of Aoyama fails to disclose "a therapeutically effective dose" of the specific compound luteolin for any purpose, much less any evidence this specific compound necessarily would be useful for preventing or treating any features of asthma, as in the presently claimed method. Even inherent anticipation requires that the "missing characteristic is necessarily present, or inherent, in the single anticipating reference." Schering Corp. v. Geneva Pharms., Inc., 1377 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). See also Toro Co. v. Deere & Co., 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."). Here, the claimed method is not sufficiently described or enabled, at least because the disclosure does not teach the effects of any dose of luteolin *in vivo*.

Further, the Examiner is respectfully remeinded that, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing

described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' "

Finally, in relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original) (Applicant's invention was directed to a biaxially oriented, flexible dilation catheter balloon (a tube which expands upon inflation) used, for example, in clearing the blood vessels of heart patients). The examiner applied a U.S. patent to Schjeldahl which disclosed injection molding a tubular preform and then injecting air into the perform to expand it against a mold (blow molding). The reference did not directly state that the end product balloon was biaxially oriented. It did disclose that the balloon was "formed from a thin flexible inelastic, high tensile strength, biaxially oriented synthetic plastic material." Id. at 1462 (emphasis in original). The examiner argued that Schjeldahl's balloon was inherently biaxially oriented. The Board reversed on the basis that the examiner did not provide objective evidence or cogent technical reasoning to support the conclusion of inherency).

Applicant respectfully submits that the Examiner has not explained how the above requirements of inherent anticipation are met in the present case, where the cited art fails to necessarily disclose or otherwise teach any therapeutic effect of any dosage of luteolin, for asthma or any other condition, as opposed to just a suggested dosage of an uncharacterized extract which may or may not have contained luteolin.

As to the rejection for alleged obviousness, Applicant notes that the cited art must provide both a suggestion to combine the disclosures so as to disclose the claimed combination, and also a reasonable expectation of success in making the claimed combination. Here, the secondary references do not make up for the failure of Aoyama to disclose a therapeutic dose of luteolin for preventing and/or treating asthma. For instance, Nagai does not disclose, teach or teach suggest use of luteolin per se for treatment or prevention of asthma, as presently claimed. Instead, Nagai actually suggests only that, ['a]s a compound strongly inhibiting the delayed phase [], it provides useful hints for the development of new drugs." In other words, Nagai at best provides an invitation to experiment with the structure of luteolin for "development of new drugs," not a suggestion or guidance on using luteolin in a method for preventing and/treating asthma, as presently claimed. Similarly, Park speaks only to the effects IL-5; again, there is no teaching of a method of treating asthma *in vivo*, and no indication that these effects of the drug, are sufficient to predict efficacy against early or late response features in asthma patients. Likewise, Kimata discloses only effects of treating human cultured mast cells, and provides no indication that these effects of the drug, are sufficient to predict efficacy against early or late response features in asthma patients.

At the time the invention was made, therefore, the present claims would not have been obvious over Aoyama combined with the other cited art because the combination would not have suggested to one of ordinary skill in the art how to use luteolin per se, or what dosage to try if so motivated; and there was insufficient evidence of efficacy *in vivo* against asthma to provide a reasonable expectation of success.

Claims 1-13 are rejected under 35 U.S.C. 102(b) as anticipated by Peng et al. (U) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Peng et al. (U) in view of Nagai (V), Park et al. (W), and Kimata et al. (X).

As explained above, the disclosure of Peng et al. cannot anticipate present Claim 1, at least because it fails to disclose "a therapeutically effective dose" of luteolin as specified in the claim, by failing to provide any evidence that this compound necessarily would be useful for preventing or treating any features of asthma, the inflammatory disease, as required in the presently claimed method. Again, Applicant would like to respectfully remind the Examiner that anticipation, even inherent anticipation, requires that the "missing characteristic is necessarily present, or inherent, in the single anticipating reference." 339 F.3d at 1377, 67 USPQ2d at 1668.

As for Aoyama, above, Applicant respectfully submits that the Examiner has not explained how the above requirements of inherent anticipation are met in the present case, where the cited art fails to necessarily disclose or otherwise provide any evidence that this compound necessarily would be useful for preventing or treating any features of asthma, the inflammatory disease, as required in the presently claimed method.

As to the rejection for alleged obviousness, Applicant notes that the cited art must provide both a suggestion to combine the disclosures so as to disclose the claimed combination, and also a reasonable expectation of success in making the claimed combination. Here again, the secondary references do not make up for the failure of Peng to disclose a therapeutic dose of luteolin for preventing and/or treating asthma, as explained above for Aoyama.

CONCLUSION

Claims 1-13 are believed allowable and an early notice to such effect is earnestly solicited. Should the Examiner have any questions or comments regarding the foregoing Amendment, he is urged to telephone the undersigned attorney.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees that may be required for the timely consideration of this Amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. 09-0528.

Respectfully submitted,

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Date

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